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Acute effects of cocaine and cannabis on response inhibition in humans: an ERP investigation

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ABSTRACT

Substance abuse has often been associated with alterations in response inhibition in humans. Not much research has examined how the acute effects of drugs modify the neurophysiological correlates of response inhibition, or how these effects interact with individual variation in trait levels of impulsivity and novelty seeking. This study investigated the effects of cocaine and cannabis on behavioural and event-related potential (ERP) correlates of response inhibition in 38 healthy drug using volunteers. A double-blind placebo-controlled randomized three-way crossover design was used. All subjects completed a standard Go/NoGo task after administration of the drugs. Compared with a placebo, cocaine yielded improved accuracy, quicker reaction times and an increased prefrontal NoGo-P3 ERP. Cannabis produced opposing results; slower reaction times, impaired accuracy and a reduction in the amplitude of the prefrontal NoGo-P3. Cannabis in addition decreased the amplitude of the parietally recorded P3, while cocaine did not affect this. Neither drugs specifically affected the N2 component, suggesting that pre-motor response inhibitory processes remain unaffected. Neither trait impulsivity nor novelty seeking interacted with drug-induced effects on measures of response inhibition. We conclude that acute drug effects on response inhibition seem to be specific to the later, evaluative stages of response inhibition. The acute effects of cannabis appeared less specific to response inhibition than those of cocaine. Together, the results show that the behavioural effects on response inhibition are reflected in electrophysiological correlates. This study did not support a substantial role of vulnerability personality traits in the acute intoxication stage.

Keywords Cannabis, cocaine, ERP, impulsivity, N2, novelty seeking, P3, response inhibition.

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INTRODUCTION

People under the influence of cannabis or cocaine exhibit changes in behaviour ranging from changes in mood to changes in cognitive processes. One of the cognitive processes often associated with the effects of drugs is the ability to inhibit pre-planned motor actions, also referred to as response inhibition. While long-term effects of various classes of drugs often lead to impaired response inhibition (Smith *et al.* 2014), the acute drug effects can lead to either impairment or improvement depending on the drug. Cannabis and cocaine are the two most commonly used drugs in Europe (EMCDDA, 2014) with quite distinct behavioural and pharmacological effects. The acute effects of cannabis and cocaine on response inhibition were therefore investigated in the current study.

Acute cannabis administration has quite consistently been shown to result in impaired response inhibition (Hart *et al.* 2001; Ramaekers *et al.* 2006; Borgwardt *et al.* 2008; Atakan *et al.* 2013; van Wel *et al.* 2013). In contrast, acute cocaine administration appears to improve the ability to suppress actions (Fillmore, Rush & Hays 2005, 2006; Garavan, Kaufman & Hester 2008; Spronk *et al.* 2013). However, until now, no study has investigated the neural correlates of response inhibition in a Go/NoGo response inhibition task. The neurophysiological underpinning of response inhibition can be investigated with

event-related potentials (ERPs). ERPs are derived from the electroencephalogram (EEG) and offer an objective basis for investigating drug effects on behaviour (Kenemans & Kähkönen 2011). With ERPs, it is possible to uncover aspects of response inhibition that cannot be detected with behavioural measures alone such as successful inhibition of NoGo trials. Moreover, because ERPs have a high temporal resolution, we are able to investigate drug effects on different sub-processes related to response inhibition.

Two event-related potentials have consistenly been associated with response inhibition: the NoGo-N2 and NoGo-P3, although their exact functional interpretation is still a matter of debate (Huster *et al.* 2013). The NoGo-N2 is a negative deflection over frontal regions and occurs between 250 and 350 ms after stimulus onset (Pfefferbaum *et al.* 1985). The NoGo-N2 is assumed to reflect top-down inhibition of a pre-response motor programme (Falkenstein, Hoormann & Hohnsbein 1999). Some authors have proposed that the NoGo-N2 reflects response conflict arising from competition between execution and inhibition of a motor action (Nieuwenhuis *et al.* 2003; Donkers & van Boxtel 2004). The NoGo-P3 is a large positive deflection, which is maximal over frontocentral electrodes, and is generated about 300–600 ms after stimulus presentation. The amplitude of the NoGo-P3 is thought to reflect cognitive and motor inhibition (Smith, Johnstone & Barry 2008). In particular, the NoGo-P3 is often associated with a later stage of response inhibition such as evaluation of successful inhibitions and termination of the inhibition process (Bokura, Yamaguchi & Kobayashi 2001).

Several pharmacological studies on cannabis and cocaine have investigated the effects on N2 and P3 ERPs in paradigms other than the Go/NoGo paradigm. In relation to cannabis, earlier findings from our own lab and others have suggested that acute THC administration, which is the main psychoactive component of cannabis, does not affect the N2 component in a flanker task or in a stop signal task (Böcker *et al.* 2010; Spronk *et al.* 2011; Theunissen *et al.* 2012; but also see Ilan *et al.* 2005 who found a reduction in N2 amplitude). In contrast, several studies employing various tasks (auditory choice, working memory and oddball tasks) have found that cannabis decreases the amplitude of the P3 ERP (Ilan *et al.* 2005; Roser *et al.* 2008; Böcker *et al.* 2010; D'Souza *et al.* 2012). In relation to cocaine, one study failed to find an effect of cocaine on the amplitude of the P3 in a continuous performance test (Herning, Hooker & Jones 1987), while an earlier one reported a decrease in P3 amplitude in an oddball task (Herning *et al.* 1985). Differences in dosages and route of administration could have contributed to the divergent findings. On the other hand, a recent review of pharmaco-ERP studies indicated that noradrenaline- and dopamine-enhancing substances increase the amplitude of the P3 ERP (Kenemans and Kähkönen 2011). This result suggests that cocaine could also increase the amplitude of P3 ERPs as it increases catecholaminergic neurotransmission (Bennett *et al.* 1995; Jones *et al.* 1995; Ritz, Cone, Kuhar, 1990; Venton *et al.* 2006). In addition, Go/NoGo ERP studies in patients with disorders characterized by dopamine deficiencies, that is, Parkinson's and Huntington's disease, have demonstrated attenuated amplitudes of the NoGo-P3 (Bokura, Yamaguchi & Kobayashi 2005; Beste *et al.* 2008; Hart *et al.* 2012) and of the NoGo-N2 (Bokura *et al.* 2005). Taken together, there seems to be a positive relation between dopamine levels and the amplitudes of the NoGo N2 and NoGo P3 ERPs.

There are individual differences in vulnerability to drug abuse and addiction. Impulsivity and sensation/novelty-seeking personality traits are among the most frequently reported. Trait impulsivity is predictive of cannabis-related problems and frequency of use (Simons & Carey 2002; Hayaki *et al.* 2011; Day *et al.* 2013). Furthermore, it is a well-established vulnerability marker for the development of substance use disorders (Verdejo-García, Lawrence & Clark 2008), as has also been demonstrated in preclinical research (Belin *et al.* 2008). Of particular relevance for the current study, trait impulsivity in rats interacts with acute cocaine effects on response inhibition, such that highly impulsive rats show the strongest benefit to response inhibition from cocaine (Dalley *et al.* 2007; Winstanley *et al.* 2009; Caprioli *et al.* 2013). Likewise, trait sensation or novelty seeking is associated with a younger age at which people first use cannabis and cocaine (Jaffe & Archer 1987; Martin *et al.* 2002). This trait has also been positively associated with frequency of cannabis use (Woicik *et al.* 2009). Rats with a stronger tendency to explore their environment, which is taken as a measure for novelty seeking, are more sensitive to the behavioural effects of psycho-stimulants (Piazza *et al.* 1989) including cocaine (Verheij *et al.* 2008). Thus, it can be expected that impulsive and novelty-seeking individuals will experience stronger effects of cocaine on behaviour and maybe of cannabis. This might also include effects on response inhibition.

The main goal of our study was to investigate the acute effect of cannabis and cocaine on response inhibition-related ERPs. A secondary aim was to examine how trait impulsivity and trait novelty seeking would interact with acute effects of drugs. For cannabis, we expected smaller P3 amplitudes, irrespective of Go or NoGo trial types, but no effect on the N2. Given previous studies indicating that cocaine improves cognition and the seemingly positive relation between dopamine levels and inhibition-related ERPs, we expected increased NoGo-N2 and prefrontal NoGo-P3 ERPs. In terms of individual differences, we hypothesized that individuals

scoring high on impulsivity and novelty seeking would be more sensitive to cognitive enhancing effects of stimulants, while a hypothesis about cannabis is less clear. The study will explore a possible association.

METHODS

Subjects

Forty-one healthy regular (non-addicted) polydrug users were recruited through advertisements on the Internet, university campuses and word-of-mouth referrals. On the first screening visit, subjects gave informed consent, received a medical examination including assessment of blood and urine samples for standard chemistry and haematology, electrocardiogram (ECG) and interview of medical history. Inclusion criteria were age, 18–40 years; regular cannabis use, i.e. two or more times per week; cocaine use, i.e. more than five times in the previous year; free from psychotropic medication; good physical health; normal weight (body mass index 18–28); and written informed consent. Exclusion criteria were substance or alcohol dependence based on DSM-IV criteria and as assessed with the M.I.N.I. plus (Sheehan *et al.* 1998); presence or history of neurological disorder as assessed during a clinical interview; pregnancy or lactation; cardiovascular abnormalities as measured by ECG; hypertension; and excessive drinking (>20 units per week) or smoking (>20 cigarettes per day). All subjects were asked to abstain from caffeine and nicotine on the testing day and from cannabis and alcohol at least 24 hours prior to each testing day. Three subjects were excluded; one withdrew consent after the first testing day, one had a cardiovascular reaction to the blood draw and study discontinuation was decided by the investigators, and one did not adhere to the abstinence instructions as confirmed by high baseline cannabinoid levels for each testing day. Of the remaining 38, seven subjects did not complete the Go/NoGo task in the cannabis condition because of adverse reactions or refusal by the subject. The subject characteristics are provided in Table 1.

This study was part of a larger multicentre trial in which participants performed numerous psychological tests on cognitive control and impulsivity (see Dutch Trial Register, trial number NTR2127; results will be published elsewhere). The study was conducted according to the code of ethics on human experimentation established by the Declaration of Helsinki (1964) and amended in Seoul (2008), and was approved by the Medical Ethics Committee of Maastricht University and the Radboud University Medical Center. A permit for obtaining, storing and administering cocaine and cannabis was obtained from the Dutch Drug Enforcement Administration.

Table 1 Subject characteristics and use history in mean and standard deviation (SD) unless otherwise stated ($n = 38$).

Variable	*Mean (SD)*
Age, years	22.1 (4.6)
Sex (F/M)	9/29
Trait impulsivity (BIS, $n = 36$)[a]	69.8 (9.2)
Trait novelty seeking (TCI, $n = 36$)[a]	25.9 (4.9)
Cannabis use, joints per week	5.5 (4.8)
Cocaine use, occasions past year	11.6 (12.5)
Alcohol use (drinks per week, $n = 38$[b])	11.8 (6.2)
Nicotine (cigarettes per day, $n = 35$[b])	9.4 (6.1)
Amphetamine (occasions past year, $n = 27$[b])	8.5 (11.8)
MDMA (XTC, occasions past year, $n = 35$[b])	7.6 (4.9)
Hallucinogen use (occasions past year, $n = 29$ [b])	6.5 (9.9)
GHB use (occasions past year, $n = 15$[b])	9.2 (7.6)

[a]*n* reflects the number of subjects for which data were available and the average was based on.
[b]*n* reflects the number of subjects who reported to use the substance. Means and SDs are based on that number (history of use data was available for all subjects).

Design

This study used a double-blind double-dummy placebo-controlled randomized three-way crossover design, in which cocaine, cannabis or placebo was separately administered over three different testing days. The three possible conditions were (1) cocaine (placebo vapours/cocaine capsules), (2) cannabis (cannabis vapours/placebo capsules), (3) placebo (placebo vapours/placebo capsules). There were at least 7 days in between visits in which no other drug exposure was allowed, with the exception of cannabis, alcohol and nicotine.

Procedure

At the day of screening, subjects completed a shortened version of the Go/NoGo task and received instruction on how to use the vapourizer on the testing days. Two self-report questionnaires for the assessment of several personality traits were given to fill out at home and bring back upon the next visit: the Barratt Impulsivity Scale (BIS-11), and the Temperament and Character Inventory (TCI).

For a timeline of the procedures of the testing day, see Fig. 1. Each testing day started in the morning with a light breakfast (non-caffeinated tea or water, up to four sandwiches) and performance of a urine drug screen, pregnancy test (women only) and alcohol breathalyzer. This was followed by pre-drug (baseline) vital sign recordings, subjective questionnaires and blood draws. Subjects received a capsule containing either 300 mg cocaine HCl or placebo orally (T0), and 45 minutes later, subjects inhaled 300 μg/kg cannabis or placebo (T1). The EEG cap was applied in the 45 minutes between T0 and T1. This

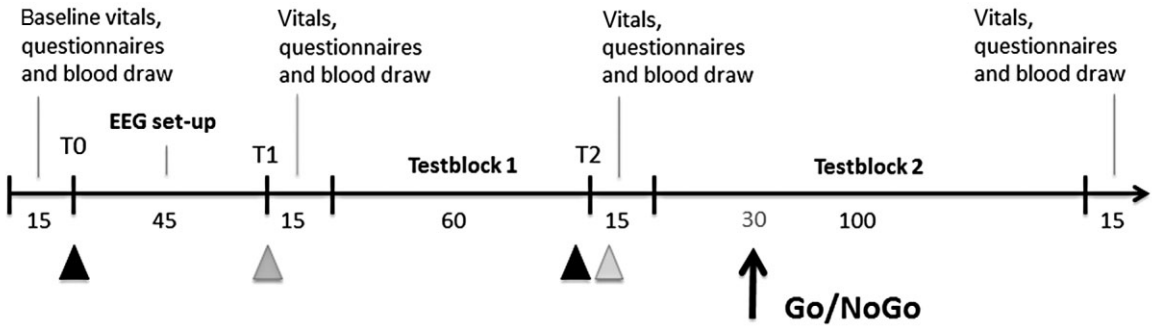

Figure 1 Timeline of the course of a testing day. Time indication is in minutes. The black triangles represent the moment of cocaine (or placebo) capsule administration and the grey triangles represent the moment of cannabis (or placebo) vapour administration. Note that in block 1 and block 2, several cognitive paradigms were performed. Those paradigms are not further discussed in the current manuscript, but will be presented elsewhere

period was taken because it takes approximately 45 minutes before adequate blood levels are reached after oral cocaine administration. After T1, the first block of behavioural tasks was assessed (test block 1). About 1 hour after T1, a second booster dose of cocaine (150 mg) or placebo followed by a second dose of cannabis 150 μg/kg or placebo was given (T2). Hereafter, the second block of behavioural tasks was assessed (test block 2). Throughout the testing day, vital sign recordings, subjective questionnaires and blood draws were obtained 5 minutes after drug administration (T1 and T2) and at the end of the testing day (blood plasma levels are reported in Supporting Information Table S1; subjective findings are reported in van Wel *et al.* 2015). An extra vital sign recording was performed before T2 to determine if the second booster could be continued.

Of the 38 subjects who completed the Go/NoGo task in the cocaine condition, 10 only received one capsule. Of those 10 subjects, five did not receive a booster session due to exceeding vital signs limits and five subjects did not receive a second cocaine dosage because the decision to give a second booster dosage was made after start of the study, and approval for this amendment had to be awaited. All our analyses were repeated without the 10 subjects who did not get the booster administration. The results without those 10 subjects showed the same pattern of significant effects for the Go reaction times, N2 amplitude and latency results, and P3 latency results. For the error rates and P3 amplitudes, the results showed a similar pattern albeit some of the tests were now only marginally significant. Because the results were in the same direction, the analyses on all subjects are here reported.

Study drugs

The cannabis use in the study was obtained from flowers of *Cannabis sativa*, grown according to good manufacturing practice (GMP)-compliant procedures (FarmalyseBV, Zaandam, the Netherlands). As placebo for cannabis, a herbal mixture containing hemp flowers was used. Two subsequent dosages of cannabis (T1: 300 μg/kg, T2: 150 μg/kg) or placebo were administered. Placebo and cannabis were administered by means of using a Volcano® vapourizer (Storz-Bickel GmbH, Tüttlingen, Germany). Five minutes before administration, cannabis was vapourized at a temperature of 225°C and the vapour was stored in a polythene bag equipped with a valved mouthpiece, preventing the loss of cannabis vapour in between inhalations. Subjects were not allowed to speak, and were instructed to inhale deeply and hold their breath for ten seconds after each inhalation. Subjects were instructed to take as much time as needed in order to minimize the occurrence of adverse events. The cocaine HCl was purchased from Mallinckrodt Pharmaceuticals (St Louis, MO, USA) and encapsulated and tested by Basic Pharma (Geleen, The Netherlands) according to GMPs. Cocaine HCl was encapsulated in opaque capsules, which were taken orally with 150 ml of water. Matching placebo capsules contained only filling material of equivalent weight.

Trait impulsivity and novelty seeking

Self-report trait impulsivity was assessed with the Dutch version of the BIS-11 (Barratt 1985; Patton, Stanford & Barratt 1995). The BIS-11 consists of 30 items yielding a total score, and additional scores for three subcategories. The novelty-seeking personality trait was measured with the Dutch version of the TCI (Cloninger *et al.* 1993). The TCI consists of 240 items. The novelty-seeking subscale was assessed by the total score of 40 items. Questionnaire data were missing for two subjects.

Go/NoGo task

Subjects had to focus on the centrally located target letter and had to press with their index finger on a response key

upon presentation of the letter X (Go trial) and to withhold their response upon appearance of the O (NoGo trial). The letters were white on a black background and the stimuli size was 0.7 by 0.7 cm. Each stimulus was displayed for 100 ms followed by a random intertrial interval between 1000 and 2000 ms. The stimuli were presented in three blocks of 150 trials and consisted of 70% Go trials and 30% NoGo trials, which were randomly intermixed. The response consisted of pressing a customized response button box. Subjects were instructed to respond as fast as possible with the index finger of the hand of preference, which was resting on the response button. Although subjects could use their hand of preference, they had to use the same hand across the three testing days. All stimuli were presented with Presentation software package (Neurobehavioral Systems, Davis, CA, USA). The Go/NoGo task was assessed in Block 2 about 45 minutes after T2 (see also Fig. 1). Psychotropic effects of cannabis reach a maximum after 15–30 minutes and were already declining, but still within range of psychoactive effects that can last up to several hours (Grotenhermen 2003). Peak levels of psychoactive effects of oral cocaine reach a maximum after approximately 1 hour (Fillmore, Rush & Hays 2002; for a review, Bigelow & Walsh 1998). The Go/NoGo was about 45 minutes after the second booster administration and thus around expected peak effects for subjects who received the second booster administration.

EEG recording

The EEG was recorded from 32 electrodes active electrodes (ActiCap, Brain Products, Munich, Germany) in accordance with the international 10–20 system. All electrodes were referenced to the left mastoid, but were later offline re-referenced to the average of both mastoids. The ground was placed on the nose. The vertical electro-oculogram (EOG) was recorded bipolarly from electrodes placed above and below the right eye. The horizontal EOG was also recorded bipolarly from electrodes lateral to each eye. All electrode impedances were kept below 50 kΩ at the start of the recording session and monitored during the test session. All signals were digitized with a sampling rate of 500 Hz and filtered offline with a band-pass of 0.01–30 Hz. Prior to running an independent component-based (ICA) EOG correction, a crude artefact rejection procedure was performed to remove large drifts and extreme low voltage signal. Stimulus-locked event-related potentials were computed separately for correct Go and NoGo stimuli, starting 200 ms before and ending 600 ms after stimulus onset. Segments were baseline corrected to a 200 ms pre-stimulus interval. Trials with reaction times faster than 100 ms (<0.15%) were removed from the data sets as they reflect anticipatory responses. Segments exceeding ±75 μV were rejected. The N2 component was defined on Go and NoGo stimulus-locked subject averages by subtracting the most negative peak in the 200–350 ms time window after stimulus onset from its preceding positive peak at electrode FCz, where N2 amplitudes were largest and in line with previous literature (Nieuwenhuis *et al.* 2003). The P3 was defined as the most positive deflection occurring in the 300–600 ms post-stimulus time window relative to baseline. Local minima (N2) or maxima (P3) were used for peak picking. Based on grand average topographies, peak amplitudes and latencies for the Go-P3 were determined at Pz and for the NoGo-P3 at FCz.

Statistical analyses

For behavioural performance, mean RTs for correct Go responses, individual percentages of commission (false alarms to NoGo trials) and omissions errors (misses to Go trials) were calculated. All analyses were conducted using a linear mixed model (LMM) using SPSS. Linear mixed modeling was chosen in order to keep subjects for whom no three complete drug conditions were available on the assumption incomplete data were missing at random. The percentages of commission and omission errors were analyzed with *Drugs* (cocaine, placebo, cannabis), *Trialtype* (Go, NoGo) as fixed factors and *Subject* as random factor. The Go trial RTs were analyzed with *Drugs* (cocaine, placebo, cannabis) as fixed factor and *Subject* as random factor. The N2 and P3 amplitude and latencies were separately analyzed with *Drugs* (cocaine, placebo, cannabis), *Trialtype* (Go, NoGo) and *Electrode* (FCz, Pz, for P3 analyses only) as fixed factors and *Subject* as random factor. In seven EEG data sets (2 cocaine, 4, placebo, 1 cannabis) markers were not correctly subscribed in the data and hence those data sets could not be included in the ERP analyses. Behavioural data were kept in the other analyses. We calculated drug-induced differences on the NoGo-N2 amplitude, prefrontal NoGo-P3 amplitude and commission errors by subtracting the value under acute drug influence (cocaine or cannabis) from placebo. Pearson correlation coefficients were calculated between these difference scores and individual trait levels (total score BIS-11, attention, motor and planning subscales, and TCI novelty-seeking scores) with a significance criterion of $P < 0.05$, two-tailed. Indices of history of use (frequency and years) were examined in the same manner. In addition, the relations between indices of history of use and performance under placebo were investigated for commission errors, and the amplitude and latency of the NoGo-N2 and NoGo-P3. Given the explorative nature of the correlational analyses, no corrections were applied.

RESULTS

Performance results

The mean percentages of error rates and reaction times across drug conditions are shown in Table 2. The LMM on percentage of error rates revealed a robust main effect of *Trialtype* ($F_{1,\ 171.529}$) = 122.9, $P < 0.001$), indicating that subjects made more commission compared with omission errors [13.4% (SD: 10.3) versus 3.6% (SD: 5.7)]. Moreover, there was a significant interaction between *Drugs* and *Trialtype* ($F_{(2.171.532)} = 3.44$, $P = 0.034$). Pairwise comparisons showed that subjects made more commission errors in the cannabis compared with the placebo and cocaine condition and fewer commission errors in the cocaine compared with the placebo condition (all *P*s < 0.022). For the omission errors, there were no differences between each drug and placebo (all *P*s > 0.130), although subjects made more omission errors in the cannabis compared with the cocaine drug condition ($P = 0.003$). The analyses on the correct Go trial reaction times showed a significant main effect of *Drugs* ($F_{(2,33.512)} = 33.5$, $P < 0.001$). Subjects responded faster in the cocaine condition compared with the cannabis and placebo condition and slower in the cannabis compared with placebo condition (all *P*s < 0.001).

ERP results

N2 ERP

Figures 2 and 3 show the grand average waveforms and the topographical maps for the Go and NoGo ERPs. Analysis on the amplitude of the N2 component revealed a significant main effect for *Trialtype* ($F_{1,\ 158.593} = 52.5$, $P < 0.001$). The N2 amplitude was larger in the NoGo compared with the Go trials (5.8 μV, SD: = 2.6 versus 3.9 μV, SD: 2.1). There was neither a significant main

Table 2 Means and SDs of percentage of errors and Go reaction times as a function of drug condition.

	Cocaine	*Placebo*	*Cannabis*
Commission error rate (%)	7.8 ± 6.4	14.5 ± 10.5	18.8 ± 11.0
Omission error rate (%)	0.9 ± 1.3	4.0 ± 6.7	6.3 ± 6.5
Reaction time Go (ms)	324 ± 28	348 ± 36	375 ± 50

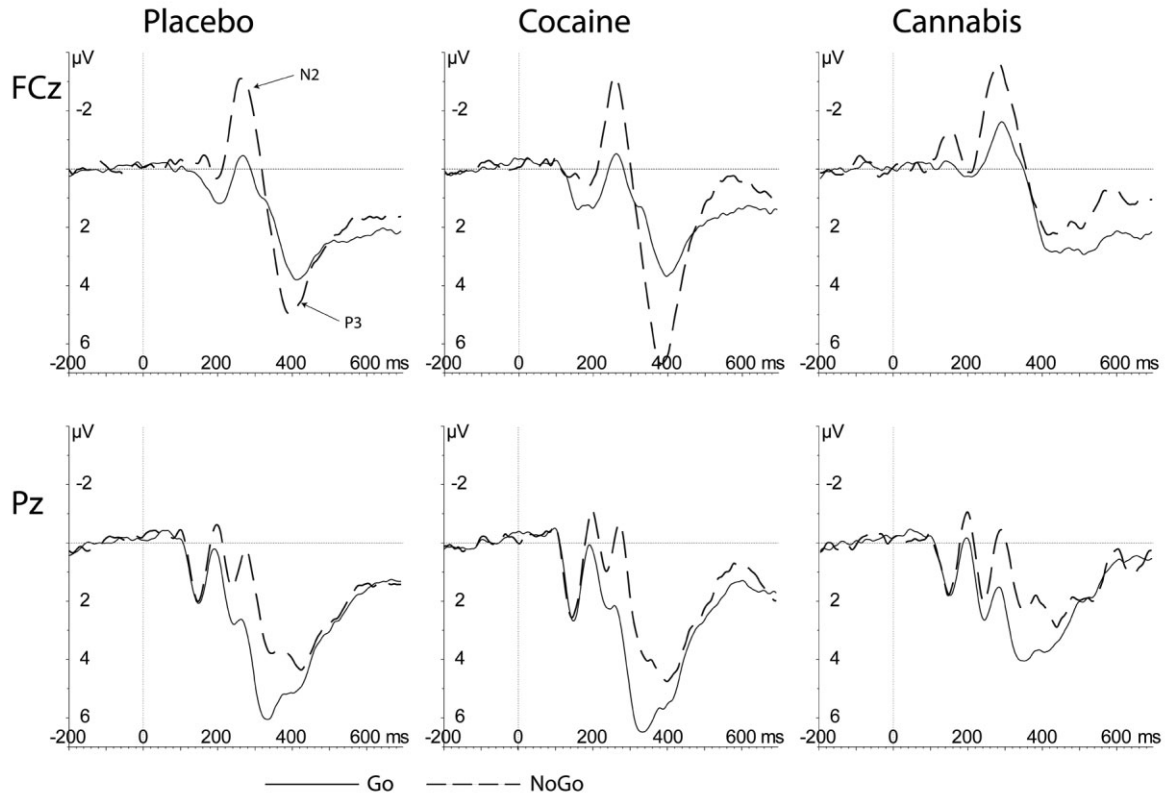

Figure 2 Grand-average stimulus-locked waveforms for correct Go and NoGo trials at FCz and Pz for the placebo, cocaine and cannabis drug conditions

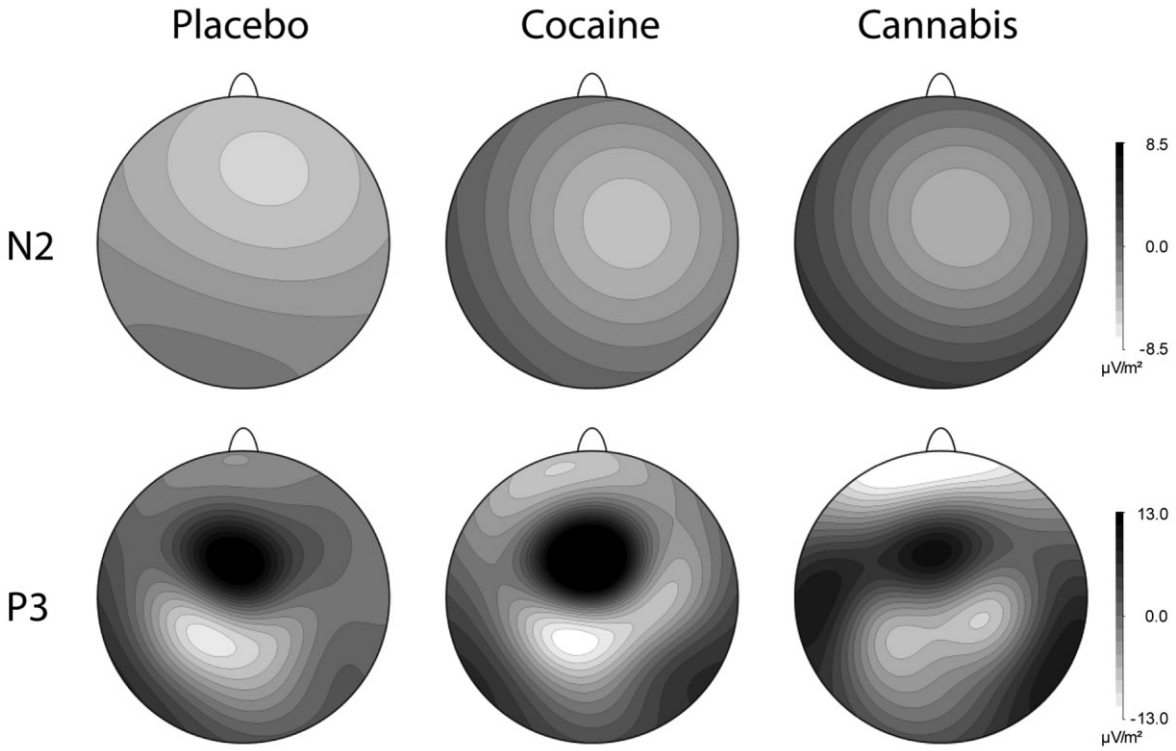

Figure 3 Topographical maps of the NoGo–Go differences waveforms for the N2 and P3 ERPs at peak amplitudes for the placebo, cocaine and cannabis drug conditions

effect for *Drugs* ($F_{2,\ 161,952} = 1.9$, $P = 0.16$), nor a significant *Drugs* × *Trialtype* interaction ($F_{2,\ 158,593} = 0.10$, $P = 0.91$), indicating that drugs did not affect the N2 amplitude in any manner. With regard to the N2 latency, there was no significant main effect for *Drugs* ($F_{2,\ 165,644} = 3.0$, $P = 0.053$), although there was a trend for the N2 peak to occur earlier in the cocaine compared with the cannabis condition (259 ms, SD: 38 versus 273 ms, SD: 42; $P = 0.094$). Furthermore, there was no main effect for *Trialtype* ($F_{1,\ 160,133} = 2.4$, $P = 0.13$), nor was there a significant *Drugs* × *Trialtype* interaction ($F_{2,\ 160,133} = 0.094$, $P = 0.91$).

P3 ERP

In regard to the P3 ERP, there was a significant *Trialtype* × *Electrode* interaction ($F_{1,\ 352,988} = 21.0$, $P < 0.001$). As expected, pairwise comparisons within each level of electrode demonstrated that the P3 amplitudes were significantly larger for the NoGo compared with the Go trials at FCz (6.5 μV, SD: = 4.8 versus 5.0 μV, SD: 4.0; $P < 0.001$), while for electrode position Pz, the opposite was found; P3 amplitudes were larger at Go compared with NoGo trials (6.7 μV, SD: 2.8 versus 5.5 μV, SD: 3.4; $P < 0.001$).

Most relevantly, there was a significant *Drugs* × *Trialtype* × *Electrode* interaction ($F_{2,\ 352,988} = 3.0$, $P = 0.049$). We further evaluated this by within-electrode analyses of the *Drugs* × *Trialtype* interaction. For the frontal-central electrode position (FCz), a significant Drugs × *Trialtype* interaction was demonstrated ($F_{2,\ 158,714} = 4.9$, $P = 0.009$). Pairwise comparisons demonstrated that the average NoGo P3 in the cocaine drug condition was larger compared with placebo (8.2 μV, SD: 5.3 versus 6.6 μV, SD: 4.5; $P = 0.032$) and that the average NoGo P3 was smaller in the cannabis compared with the placebo drug condition (4.3 μV, SD: 4.2 versus 6.6 μV, SD = 4.5; $P = 0.036$). No drug effects for prefrontally recorded Go trials were observed (all Ps > 1.0). For the parietally recorded P3 at Pz, no significant *Drugs* by *Trialtype* interaction was demonstrated ($F_{2,\ 159.526} = 0.18$, $P = 0.83$). The observed main effect for *Drugs* ($F_{2,\ 161.464} = 17.2$, $P < 0.001$) nonetheless revealed overall drug effects on the P3. More specifically, the P3 amplitude as recorded from Pz was significant smaller in the cannabis condition (4.8 μV, SD: 2.8) compared with placebo and cocaine (6.3 μV, SD: 2.6 and 6.9 μV, SD: 3.7; all Ps < 0.001). The P3 amplitude at Pz did not differ between cocaine and placebo ($P = 0.16$).

Analyses of the P3 latency revealed that the three-way *Drugs* × *Trialtype* × *Electrode* interaction ($F_{2,\ 353,965} = 0.83$, $P = 0.44$) was not significant. In addition, neither the two-way *Drugs* × *Electrode* two-way interaction

($F_{2,\ 353,965} = 2.5$, $P = 0.084$), nor the two-way *Drugs* × *Trialtype* were significant ($F_{2,\ 353,965} = 0.22$, $P = 0.81$). Together, these results indicate that *Drugs* do not differentially affect P3 latencies across different levels of electrode locations or *Trialtypes*. However, there were a few significant main effects. Of most relevance, there was a main effect of *Drugs* ($F_{2,\ 360,823} = 36.7$, $P < 0.001$) that was due to a slower P3 latency in cannabis compared with placebo condition (442 ms, SD: 71 versus 403 ms, SD: 66; $P < 0.001$) and a shorter latency in cocaine compared with placebo (387 ms, SD: 55 versus 403, SD: 66; $P = 0.029$). Furthermore, latencies were shorter in Go than in NoGo trials (400 ms, SD: 75 versus 418 ms, SD: 58) and at parietal electrode versus prefrontal electrode sites (394 ms, SD: 65 versus 423 ms, SD 67) as indicated by significant main effects (*P*s < 0.001).

Individual differences in impulsivity and novelty seeking

Trait impulsivity and novelty seeking were highly positively correlated ($r = 0.58$, $P < 0.001$). There were no correlations between trait personality levels of impulsivity or novelty seeking and drug-induced (i.e. placebo minus cannabis or placebo minus cocaine) effects on commission errors, NoGo N2 ERP amplitude or NoGo P3 amplitude (all *P*s > 0.14). We also explored if the three subscales of the BIS-11 (attention, motor impulsivity, planning) were associated with drug-induced effects on response inhibition. For none of the three subscales, any significant relations with drug-induced effects on response inhibition were observed (all *P*s > 0.11).

Frequency and years of use measures were used to explore if drug-induced effects on response inhibition were associated with history of use. History of use measures for cannabis (joints per week/years of cannabis use) were not correlated with any of the cannabis-induced effects on response inhibition measures (all *P*s > 0.34). Likewise, there were no significant associations between cocaine-related history of use measures (occasions past year/years of cocaine use) for any of the cocaine-induced effects on response inhibition (all *P*s > 0.16).

Finally, we explored if there were any relations between performance in the placebo condition and any of the history of use measures. Results indicated that none of the associations between commission errors, NoGo-N2 amplitude or NoGo-P3 amplitude and history of use measures were significant (*P*s > 0.31). Notably, a higher frequency of cannabis use appeared to be related with longer Go reaction times ($r = 0.44$, $P = 0.006$), and longer latencies for the NoGo-N2 ($r = 0.334$, $P = 0.054$) and NoGo-P3 ($r = 0.35$, $P = 0.043$).

DISCUSSION

Cocaine caused an improvement in response inhibition as indicated by a decrease in the number of commission errors and a faster reaction time. Cannabis, in contrast, impaired response inhibition; the number of commission errors increased, and reaction time slowed down. There were generally more omission errors after cannabis compared with cocaine, although neither drug differed from placebo. Most importantly, in regard to the ERPs, neither drug affected the amplitude of the prefrontally recorded N2. Further, cocaine enhanced the amplitude of the response inhibition-related prefrontal NoGo P3 while leaving the parietal Go P3 unaffected. Cannabis decreased the amplitude of the prefrontal NoGo P3 and caused an overall reduction of the parietally recorded P3 ERP. Furthermore, cocaine caused a shorter P3 latency while cannabis prolonged it. Drug-induced effects on response inhibition were not dependent on individual differences in trait impulsivity and novelty seeking.

The behavioural results in the cannabis condition are consistent with a large number of studies that have demonstrated the impairing effects of cannabinoids on response inhibition (Hart *et al.* 2001; Ramaekers *et al.* 2006; Borgwardt *et al.* 2008; Atakan *et al.* 2013; van Wel *et al.* 2013). Alcohol also consistently impairs response inhibition (Ramaekers & Kuypers 2006; Dougherty *et al.* 2008) suggesting a common effect on response inhibition across two very commonly used substances. Notably, although not among the primary aims of research, the exploratory analyses on reaction times and latencies showed a positive relation between frequency of cannabis use and slowing of responses/occurrence of electrophysiological response inhibition correlates.

The observed behavioural improvement in response inhibition following cocaine is in line with acute cocaine studies in humans that have shown decreased stop signal reaction times and fewer commission errors (Fillmore *et al.* 2005, 2006; Garavan *et al.* 2008). An important observation is that this benefit contrasts with the impairing effects of cocaine that are seen after prolonged use (Pike *et al.* 2013; see also Spronk *et al.* 2013). The findings in the cocaine condition differ from a recent large study from our own lab, in which we observed an increased failure of inhibition in a stop signal task (van Wel *et al.* 2013). The Go/NoGo task involves inhibition of a prepotent response tendency, while the stop signal task requires inhibition of an already initiated response, and might thus tap into different aspects of response inhibition (Verbruggen & Logan 2008; Swick, Ashley & Turken 2011). Another explanation might be related to the specific stop signal task version that was being used. In contrast to common practice, the used stop signal task did not employ dynamically adjusted stop-signal delay times. It is

therefore possibly that the speeding of reaction times might have led to the increased error rates in the stop signal task. In other words, subjects might have been 'too fast' to anticipate a possible stop signal as the response has already been executed. Taken together, the effects of cocaine might be different for various response inhibition sub-domains and might be determined by specific details of the paradigms used.

Alternatively, differences in dosing might have contributed to the divergence in results. The stop signal task performance was assessed at peak levels of 300 mg of oral cocaine, while the Go/NoGo in the current study was assessed at peak levels of the booster dosage of 150 mg. There is a possibility that differences in dosages might have contributed to the effects. In general, there is very little information on dose–response relationships between cocaine and cognition. However, cocaine's effect on response inhibition was previously shown to follow an inverted U-shape relation (Fillmore *et al.* 2006). In this study, response inhibition improved after administration of the relative lower dosages (100, 200 mg) while impairment was observed after 300 mg of oral cocaine.

In addition, cocaine caused speeding of Go reactions, while cannabis caused slowing of Go reactions. These finding on reaction times were also corroborated by the drug effects on the latencies of the P3 ERPs. Given that the reaction time effects are accompanied by a respective decrease and increase in error rates, it is unlikely that speed-accuracy trade-offs played a role. Rather, the slowing or speeding of reaction time after drugs might indicate that people are trying to compensate for or adapt to poor performance (after cannabis) or are encouraged/reinforced by good performance (cocaine). Alternatively, the drug effects on psychomotor performance could possibly act on the performance of this task in an independent manner.

The present study extends earlier behavioural findings by including electrophysiological correlates of response inhibition. The prefrontally recorded NoGo-P3 ERP was decreased after cannabis and is thus in agreement with the observed impaired response inhibition on the behavioural level. In particular, the NoGo-P3 ERP is associated with evaluation of the response inhibition process (Huster *et al.* 2013) and a decrement suggests that cannabis impairs this evaluation process. Our data showed that cannabis also reduced the parietally recorded P3 ERP. This finding was unsurprising given that several studies have demonstrated that cannabinoids decrease the amplitude of the parietal P3 amplitude (Ilan, Smith & Gevins 2004; Roser *et al.* 2008; Böcker *et al.* 2010). The parietally recorded P3 is known to be related to response activation and stimulus evaluation (Eimer 1993; Polich 2007). Therefore, the results suggest that the cannabis effects on the inhibition-related NoGo P3 is not unique, but instead covaries with the extent of the effects of the drugs on response activation or stimulus evaluation.

Enhancement of the prefrontal NoGo-P3 does not only occur after cocaine, but also after similar drugs, such as methylphenidate and d-amphetamine (for a review: Kenemans & Kähkönen 2011). The NoGo-P3 might therefore be dependent on the stimulant and dopamine-enhancing properties of substances. Enhanced NoGo-P3 amplitude is also consistent with studies showing that higher task demands are related to higher NoGo-P3 amplitudes (Dimoska, Johnstone & Barry 2006; Smith, Johnstone & Barry 2006, 2007). Of particular interest is the study by Dimoska *et al.* (2006) that reported that the prefrontal NoGo-P3 amplitude was larger in fast compared with relatively slow responders. Our behavioural results showed that cocaine caused a speeding in reaction times. Arguing along similar lines, it is possible that this speeding has caused a more demanding task setting, and has led to larger NoGo-P3s because of a stronger recruitment of inhibitory processes in order to timely inhibit responding to the NoGo stimulus.

The amplitude of the N2 ERP was not affected by either drug. The absence of an effect on the N2 after cocaine and cannabis suggests that neither pre-motor response inhibition processes, nor conflict monitoring, is altered by the drug. Interestingly, earlier acute administration studies with alcohol and cannabinoids also showed that the N2 amplitude (when measured in a neutral task condition) was unaffected (Theunissen *et al.* 2012; Korucuoglu, Gladwin & Wiers 2014; Stock *et al.* 2014). This suggests that across several classes of drugs of abuse, effects on response inhibition might be selective to a later, evaluative stage of response inhibition, while leaving pre-motor inhibition/conflict processing intact.

The neuropharmacological effects of cocaine in particular (the neuropharmacology of cannabis is more complex) could shed light on the neural substrates of response inhibition ERPs. Beste *et al.* (2010) proposed that dopamine release in the meso-cortico-limbic dopaminergic pathway underlies the generation of the NoGo P3, while dopamine release within the nigrostriatal pathways underlies the generation of the N2. Many studies have indicated that cocaine increases extracellular dopamine levels in the mesolimbic dopamine pathway in particular (Di Chiara & Imperato 1988; Carboni *et al.* 1989; Pettit *et al.* 1990). The enhancing effects on the NoGo-P3, but not the NoGo-N2 are hence consistent with cocaine's preferential involvement of enhancing dopamine levels in mesolimbic dopamine pathways. Furthermore, the current results strengthen the involvement of the meso-cortico-limbic dopamine system in the generation of the NoGo-P3.

Our data suggest that individual differences in trait impulsivity and novelty seeking are not associated with

cocaine- and cannabis-induced effects on any of the response inhibition measures. This is inconsistent with several studies that have suggested that pre-existing traits affect behavioural and neurophysiological responses to drugs (for a review, see Jupp and Dalley 2014). Various explanations could be offered for not finding influences of these two personality traits. Many recent and influential studies on acute administration and pre-existing traits have been performed in animals. In these studies, high impulsive and low impulsive rats are selected and thus reflect the two extremes of a continuum. In contrast, our sample is less differentiated; for example, only a small group can actually be called high impulsive according to the scoring criteria of the questionnaire. At the same time, trait scores for impulsivity and novelty seeking are likely to be higher in drug users compared with non-using controls. Our sample therefore probably reflects a selection of subjects with questionnaire scores being in a higher than average and selected range. Research in which specifically high impulsive/high novelty-seeking individuals versus low impulsive/low novelty-seeking individuals are compared would be better suited to address the role of individual differences. Another possible reason for the failure to find an influence of the two traits is that we relied on self-report measures in the determination of the personality traits. It is known that human self-report and task-based impulsivity measures are poorly correlated (e.g. Dolan & Fullam 2004). For these reasons, self-report measures have been argued to be unsuitable for pharmacological studies (Swann *et al.* 2002). The use of task-based measures of trait impulsivity and novelty seeking would be in closer correspondence with the animal literature and be better suited for the current pharmacological study. Despite not finding moderation by impulsivity and novelty seeking, the findings do not exclude the possibility that these personality traits affect other subjective or cognitive domains not addressed in the current study.

A few limitations that could have influenced the interpretation of the results should be noted. First, the Go/NoGo task might not have always been administered at peak levels of the drugs. This is of particular concern for the cocaine condition as a number of subjects did not receive a booster dose. However, secondary analyses excluding subjects who only got one cocaine dosage did not demonstrate a different pattern of results. For cannabis, it is known that acute drug effects on cognition can outlast the period of peak levels. If anything, we believe that the impairing effects on the Go/NoGo task would have been even stronger, because plasma levels were already declining during acquisition of the Go/NoGo task. Second, the required abstinence from nicotine and caffeine in particular, could have led to withdrawal effects, which could have caused underperformance on the testing day. Third, the blinding of the drug condition was de facto unsuccessful in that both experimenters and subjects could rather adequately guess the drug conditions based on the behavioural and subjective effects during the study days. Hence, the possible influence of expectancy effects cannot be excluded. Fourth, subacute effects (effects that outlast the immediate effects of drugs) of cannabis could have been present on the testing days as the required abstinence time (24 hours) was limited. It is known that chronic use of cannabis can have behavioural effects lasting up to several days after cannabis intake (Solowij, Michie & Fox 1995). However, any residual THC concentrations were comparable across conditions (see also Supporting Information Table S1 for drug metabolites). It is therefore unlikely that the possible presence of subacute drug effects has affected the relative differences between acute drug effects on cognition. Larger abstinence periods would have been desirable, but were infeasible in a study with moderate to heavy cannabis users. Lastly, trait impulsivity and possibly also novelty seeking in humans are known to be influenced by prolonged drug use (Vonmoos *et al.* 2013). The history of use might thus have affected or 'contaminated' the trait personality measures. One way to circumvent this limitation is to perform acute drug administration studies in drug-naïve subjects. However, administration of drugs of abuse to drug-naïve individuals is not considered feasible due to ethical concerns.

The cognitive changes following cocaine and cannabis intoxication are relevant for those on the risk of starting to take the drugs or educating users the possible risks of taking drugs. Most importantly, the current results show that drugs affect response inhibition. These observed drug effects might thus have implications for daily life activities, and, although this should be scientifically demonstrated, could possibly even contribute to motivational aspects of drug use. For example, the cognitive enhancing effects of cocaine might act as a positive reinforcer and hence contribute to its abusive potential. The impairing effects of cannabis might lead to risky and unsafe behaviour, for example, in motoring and operating machines, as one might not respond in time to signs that one should inhibit an impulse. It might also contribute to subsequent drug use as self-monitoring processes that are required to timely stop smoking are compromised. As cannabis' effects on cognition might be long lasting, it is important to consider these side effects, when one has to engage in cognitively demanding activities such as driving.

In conclusion, this study demonstrates that acute administration of two substances from two different classes of drugs of abuse affect response inhibition in opposing manners. Specifically, cannabis impaired behavioural measures of response inhibition, resulted in a general decrement of the P3 amplitude as well as a

slowing of the P3 ERPs. Cocaine resulted in improved behavioural measures of response inhibition and an increased prefrontal NoGo P3. Neither drug affected the amplitude of the N2 ERP, suggesting that early conflict/pre-motor inhibitory processes are spared by drugs. Personality trait levels as measured with the BIS-11 and the TCI did not interact with the behavioural and electrophysiological effects related to response inhibition, suggesting that they play a limited role in explaining individual differences in acute drug effects on response inhibition in humans.

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Disclosure/Conflict of Interest

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Authors Contributions

EdB, JvW, JR and RJV designed the study and wrote the protocol. DBS carried out the experiments, performed statistical analyses and wrote the first draft of the manuscript. RJV performed medical examinations and supervised the experiments. All authors contributed to and approved the final manuscript.

References

Atakan Z, Bhattacharyya S, Allen P, Martín-Santos R, Crippa JA, Borgwardt SJ, Fusar-Poli P, Seal M, Sallis H, Stahl D, Zuardi AW, Rubia K, McGuire P (2013) Cannabis affects people differently: inter-subject variation in the psychotogenic effects of Δ9-tetrahydrocannabinol: a functional magnetic resonance imaging study with healthy volunteers. Psychol Med 43: 1255–1267.

Barratt S (1985) Impulsiveness subtraits: arousal and information processing. In: Spence JT, Hard CE, eds. Motivation, Emotion, and Personality, pp. 137–146. North-Holland: Elsevier Science.

Belin D, Mar AC, Dalley JW, Robbins TW, Everitt BJ (2008) High impulsivity predicts the switch to compulsive cocaine-taking. Science 320:1352–1355.

Bennett BA, Wichems CH, Hollingsworth CK, Davies HM, Thornley C, Sexton T, Childers SR (1995) Novel 2-substituted cocaine analogs: uptake and ligand binding studies at dopamine, serotonin and norepinephrine transport sites in the rat brain. J Pharmacol Exp Ther 272:1176–1186.

Beste C, Saft C, Gold R, Falkenstein M (2008). Response inhibition in Huntington's disease—a study using ERPs and sLORETA. Neuropsychologia 46:1290–1297.

Beste C, Willemssen R, Saft C, Falkenstein M (2010) Response inhibition subprocesses and dopaminergic pathways: basal ganglia disease effects. Neuropsychologia 48:366–373.

Bigelow GE, Walsh SL (1998) Evaluation of potential pharmacotherapies: response to cocaine challenge in the human laboratory. In: Higgins ST, Katz JL, eds. Cocaine Abuse: Behavior, Pharmacology, and Clinical Applications, pp. 209–238. New York: Academic Press.

Bokura H, Yamaguchi S, Kobayashi S (2001) Electrophysiological correlates for response inhibition in a Go/NoGo task. Clin Neurophysiol 112:2224–2232.

Bokura H, Yamaguchi S, Kobayashi S (2005) Event-related potentials for response inhibition in Parkinson's disease. Neuropsychologia 43:967–975.

Borgwardt SJ, Allen P, Bhattacharyya S, Fusar-Poli P, Crippa JA, Seal ML, Fraccaro V, Atakan Z, Martin-Santos R, O'Carroll C, Rubia K, McGuire PK (2008) Neural basis of Delta-9-tetrahydrocannabinol and cannabidiol: effects during response inhibition. Biol Psychiatry 64:966–973.

Böcker KBE, Gerritsen J, Hunault CC, Kruidenier M, Mensinga TT, Kenemans JL (2010) Cannabis with high δ9-THC contents affects perception and visual selective attention acutely: an event-related potential study. Pharmacol Biochem Behav 96:67–74.

Caprioli D, Hong YT, Sawiak SJ, Ferrari V, Williamson DJ, Jupp B, Adrian Carpenter J, Aigbirhio FI, Everitt BJ, Robbins TW, Fryer TD, Dalley JW (2013) Baseline-dependent effects of cocaine pre-exposure on impulsivity and D2/3 receptor availability in the rat striatum: possible relevance to the attention-deficit hyperactivity syndrome. Neuropsychopharmacology 38: 1460–1471.

Carboni E, Imperato A, Perezzani L, Di Chiara G (1989) Amphetamine, cocaine, phencyclidine and nomifensine increase extracellular dopamine concentrations preferentially in the nucleus accumbens of freely moving rats. Neuroscience 28:653–661.

Cloninger CR, Svrakic DM, Przyeck TR (1993) A psychobiological model of temperament and character. Arch Gen Psychiatry 50:975–590.

Dalley JW, Fryer TD, Brichard L, Robinson ESJ, Theobald EH, Lääne K, Pena Y, Murphy ER, Shah Y, Probst K, Abakumova I, Aigbirhio FI, Richards HK, Hong Y, Baron JC, Everitt BJ, Robbins TW (2007) Nucleus accumbens D2/3 receptors predict trait impulsivity and cocaine reinforcement. Science 315:1267–1270.

Day AM, Metrik J, Spillane NS, Kahler CW (2013) Working memory and impulsivity predict marijuana-related problems among frequent users. Drug Alcohol Depend 131:171–174.

Di Chiara G, Imperato A (1988) Drugs abused by humans preferentially increase synaptic dopamine concentrations in the mesolimbic system of freely moving rats. Proc Natl Acad Sci U S A 85:5274–5278.

Dimoska A, Johnstone SJ, Barry RJ (2006) The auditory-evoked N2 and P3 components in the stop-signal task: indices of inhibition, response-conflict or error-detection? Brain Cogn 62:98–112.

Dolan M, Fullam R (2004) Behavioural and psychometric measures of impulsivity in a personality disordered population. J Forens Psychiatry Psychol 15:426–450.

Donkers FCL, van Boxtel GJM (2004) The N2 in go/no-go tasks reflects conflict monitoring not response inhibition. Brain Cogn 56:165–176.

Dougherty DM, Marsh-Richard DM, Hatzis ES, Nouvion SO, Mathias CW (2008) A test of alcohol dose effects on multiple behavioral measures of impulsivity. Drug Alcohol Depend 96:111–120.

D'Souza DC, Fridberg DJ, Skosnik PD, Williams A, Roach B, Singh N, Carbuto M, Elander J, Schnakenberg A, Pittman B, Sewell RA, Ranganathan M, Mathalon D (2012) Dose-related modulation of event-related potentials to novel and target stimuli by intravenous Δ^9-THC in humans. Neuropsychopharmacology 37:1632–1646.

Eimer M (1993) Effects of attention and stimulus probability on ERPs in a Go/Nogo task. Biol Psychol 35:123–138.

EMCDDA (2014). European drug report 2014: trends and developments. Lisbon.

Falkenstein M, Hoormann J, Hohnsbein J (1999) ERP components in Go/NoGo tasks and their relation to inhibition. Acta Psychol (Amst) 101:267–291.

Fillmore MT, Rush CR, Hays L (2002) Acute effects of oral cocaine on inhibitory control of behavior in humans. Drug Alcohol Depend 67:157–167.

Fillmore MT, Rush CR, Hays L (2005) Cocaine improves inhibitory control in a human model of response conflict. Exp Clin Psychopharmacol 13:327–335.

Fillmore MT, Rush CR, Hays L (2006) Acute effects of cocaine in two models of inhibitory control: implications of non-linear dose effects. Addiction 101:1323–1332.

Garavan H, Kaufman JN, Hester R (2008) Acute effects of cocaine on the neurobiology of cognitive control. Philos Trans R Soc Lond B Biol Sci 363:3267–3276.

Grotenhermen F (2003) Pharmacokinetics and pharmacodynamics of cannabinoids. Clin Pharmacokinet 42:327–360.

Hart CL, Gorp W, van Haney M, Foltin RW, Fischman MW (2001) Effects of acute smoked marijuana on complex cognitive performance. Neuropsychopharmacology 25:757–765.

Hart EP, Dumas EM, Reijntjes RHAM, Hiele K, van der Bogaard SJA, van den Middelkoop HAM, Roos RA, van Dijk JG (2012) Deficient sustained attention to response task and P300 characteristics in early Huntington's disease. J Neurol 259:1191–1198.

Hayaki J, Herman DS, Hagerty CE, Dios MA, de Anderson BJ, Stein MD (2011) Expectancies and self-efficacy mediate the effects of impulsivity on marijuana use outcomes: an application of the acquired preparedness model. Addict Behav 36:389–396.

Herning RI, Jones RT, Hooker WD, Tulunay FC (1985) Information processing components of the auditory event related potential are reduced by cocaine. Psychopharmacology (Berl) 87:178–185.

Herning RI, Hooker WD, Jones RT (1987). Cocaine effects on electroencephalographic cognitive event-related potentials and performance. Electroencephalogr Clin Neurophysiol 66:34–42.

Huster RJ, Enriquez-Geppert S, Lavallee CF, Falkenstein M, Herrmann CS (2013) Electroencephalography of response inhibition tasks: functional networks and cognitive contributions. Int J Psychophysiol 87:217–233.

Ilan AB, Gevins A, Coleman M, ElSohly MA, de Wit H (2005) Neurophysiological and subjective profile of marijuana with varying concentrations of cannabinoids. Behav Pharmacol 16:487–496.

Ilan AB, Smith ME, Gevins A (2004) Effects of marijuana on neurophysiological signals of working and episodic memory. Psychopharmacology (Berl) 176:214–222.

Jaffe LT, Archer RP (1987) The prediction of drug use among college students from MMPI, MCMI, and sensation seeking scales. J Pers Assess 51:243–253.

Jones SR, Garris PA, Wightman RM (1995) Different effects of cocaine and nomifensine on dopamine uptake in the caudate-putamen and nucleus accumbens. J Pharmacol Exp Ther 274:396–403.

Jupp B, Dalley JW (2014) Behavioral endophenotypes of drug addiction: etiological insights from neuroimaging studies. Neuropharmacology 76 (Pt B):487–497.

Kenemans JL, Kähkönen S (2011) How human electrophysiology informs psychopharmacology: from bottom-up driven processing to top-down control. Neuropsychopharmacology 36:26–51.

Korucuoglu O, Gladwin TE, Wiers RW (2014) Alcohol-induced changes in conflict monitoring and error detection as predictors of alcohol use in late adolescence. Neuropsychopharmacology 40:614–621.

Martin CA, Kelly TH, Rayens MK, Brogli BR, Brenzel A, Smith WJ, Omar HA (2002) Sensation seeking, puberty, and nicotine, alcohol, and marijuana use in adolescence. J Am Acad Child Adolesc Psychiatry 41:1495–1502.

Nieuwenhuis S, Yeung N, Wildenberg W, van den Ridderinkhof KR (2003) Electrophysiological correlates of anterior cingulate function in a go/no-go task: effects of response conflict and trial type frequency. Cogn Affect Behav Neurosci 3:17–26.

Patton JH, Stanford MS, Barratt ES (1995) Factor structure of the Barratt impulsiveness scale. J Clin Psychol 51:768–774.

Pettit HO, Pan HT, Parsons LH, Justice JB (1990) Extracellular concentrations of cocaine and dopamine are enhanced during chronic cocaine administration. J Neurochem 55:798–804.

Pfefferbaum A, Ford JM, Weller BJ, Kopell BS (1985) ERPs to response production and inhibition. Electroencephalogr Clin Neurophysiol 60:423–434.

Piazza PV, Deminiere J-M, Le Moal M, Simon H (1989) Factors that predict individual vulnerability to amphetamine self-administration. Science (80-) 245:1511–1513.

Pike E, Stoops WW, Fillmore MT, Rush CR (2013) Drug-related stimuli impair inhibitory control in cocaine abusers. Drug Alcohol Depend 113:768–771.

Polich J (2007) Updating P300: an integrative theory of P3a and P3b. Clin Neurophysiol 118:2128–2148.

Ramaekers JG, Kauert G, Ruitenbeek P, van Theunissen EL, Schneider E, Moeller MR (2006) High-potency marijuana impairs executive function and inhibitory motor control. Neuropsychopharmacology 31:2296–2303.

Ramaekers JG, Kuypers KPC (2006) Acute effects of 3,4-methylenedioxymethamphetamine (MDMA) on behavioral measures of impulsivity: alone and in combination with alcohol. Neuropsychopharmacology 31:1048–1055.

Ritz MC, Cone EJ, Kuhar M (1990) Cocaine inhibition of ligand binding at dopamine, norepinephrine and serotonin transporters: a structure-activity study. Lief Sci 46:635–645.

Roser P, Juckel G, Rentzsch J, Nadulski T, Gallinat J, Stadelmann AM (2008) Effects of acute oral Delta9-tetrahydrocannabinol and standardized cannabis extract on the auditory P300 event-related potential in healthy volunteers. Eur Neuropsychopharmacol 18:569–577.

Sheehan DV, Lecrubier Y, Sheehan KH, Amorim P, Janavs J, Weiller E, Dubar GC (1998) The mini-international neuro-

psychiatric interview (M.I.N.I.: the development and validation of a structured diagnostic psychiatric interview for DSM-IV and ICD-10. J Clin Psychiatry 59 (Suppl. 20):22–33.

Simons JS, Carey KB (2002) Risk and vulnerability for marijuana use problems: the role of affect dysregulation. Psychol Addict Behav 16:72–75.

Smith JL, Johnstone SJ, Barry RJ (2006) Effects of pre-stimulus processing on subsequent events in a warned Go/NoGo paradigm: response preparation, execution and inhibition. Int J Psychophysiol 61:121–133.

Smith JL, Johnstone SJ, Barry RJ (2007) Response priming in the Go/NoGo task: the N2 reflects neither inhibition nor conflict. Clin Neurophysiol 118:343–355.

Smith JL, Johnstone SJ, Barry RJ (2008) Movement-related potentials in the Go/NoGo task: the P3 reflects both cognitive and motor inhibition. Clin Neurophysiol 119:704–714.

Smith JL, Mattick RP, Jamadar SD, Iredale JM (2014) Deficits in behavioural inhibition in substance abuse and addiction: a meta-analysis. Drug Alcohol Depend 119:704–714.

Solowij N, Michie PT, Fox AM (1995) Differential impairments of selective attention due to frequency and duration of cannabis use. Biol Psychiatry 37:731–739.

Spronk D, Dumont GJ, Verkes RJ, de Bruijn ER (2011) Acute effects of delta-9-tetrahydrocannabinol on performance monitoring in healthy volunteers. Front Behav Neurosci 5:59.

Spronk DB, van Wel JHP, Ramaekers JG, Verkes RJ (2013) Characterizing the cognitive effects of cocaine: a comprehensive review. Neurosci Biobehav Rev 37:1838–1859.

Stock A-K, Schulz T, Lenhardt M, Blaszkewicz M, Beste C (2014) High-dose alcohol intoxication differentially modulates cognitive subprocesses involved in response inhibition. Addict Biol. doi: 10.1111/adb.12170.

Swann AC, Bjork JM, Moeller FG, Dougherty DM (2002) Two models of impulsivity: relationship to personality traits and psychopathology. Biol Psychiatry 51:988–994.

Swick D, Ashley V, Turken U (2011) Are the neural correlates of stopping and not going identical? Quantitative meta-analysis of two response inhibition tasks. Neuroimage 56:1655–1665.

Theunissen EL, Kauert GF, Toennes SW, Moeller MR, Sambeth A, Blanchard MM, Ramaekers JG (2012) Neurophysiological functioning of occasional and heavy cannabis users during THC intoxication. Psychopharmacology (Berl) 220:341–350.

van Wel JHP, Kuypers KPC, Theunissen EL, Toennes SW, Spronk DB, Verkes RJ, Ramaekers JG (2013) Single doses of THC and cocaine decrease proficiency of impulse control in heavy cannabis users. Br J Pharmacol 170:1410–1420.

van Wel JHP, Spronk DB, Kuypers KP, Theunissen EL, Toennes SW, Verkes RJ, Ramaekers JG (2015) Psychedelic symptoms of cannabis and cocaine use as a function of trait impulsivity. J Psychopharmacol 29:324–334.

Venton BJ, Seipel AT, Phillips PEM, Wetsel WC, Gitler D, Greengard P, Augustine GJ, Wightman RM (2006) Cocaine increases dopamine release by mobilization of a synapsin-dependent reserve pool. J Neurosci 26:3206–3209.

Verbruggen F, Logan GD (2008) Automatic and controlled response inhibition: associative learning in the go/no-go and stop-signal paradigms. J Exp Psychol Gen 137:649–672.

Verdejo-García A, Lawrence AJ, Clark L (2008) Impulsivity as a vulnerability marker for substance-use disorders: review of findings from high-risk research, problem gamblers and genetic association studies. Neurosci Biobehav Rev 32:777–810.

Verheij MMM, de Mulder ELW, De Leonibus E, van Loo KMJ, Cools AR (2008) Rats that differentially respond to cocaine differ in their dopaminergic storage capacity of the nucleus accumbens. J Neurochem 105:2122–2133.

Vonmoos M, Hulka LM, Preller KH, Jenni D, Schulz C, Baumgartner MR, Quednow BB (2013) Differences in self-reported and behavioral measures of impulsivity in recreational and dependent cocaine users. Drug Alcohol Depend 133:61–70.

Winstanley CA, Bachtell RK, Theobald DEH, Laali S, Green TA, Kumar A, Chakravarty S, Self DW, Nestler EJ. (2009) Increased impulsivity during withdrawal from cocaine self-administration: role for DeltaFosB in the orbitofrontal cortex. Cereb Cortex 19:435–444.

Woicik PA, Stewart SH, Pihl RO, Conrod PJ (2009) The Substance Use Risk Profile Scale: a scale measuring traits linked to reinforcement-specific substance use profiles. Addict Behav 34:1042–1055.

SUPPORTING INFORMATION

Additional Supporting Information may be found in the online version of this article at the publisher's web-site:

Table S1 Serum concentration (ng/ml) of THC, THC-COOH, THC-OH and plasma concentrations (ng/ml) of benzoylecgonine for all four time points.